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Three versus seven days to return-to-work after mild traumatic brain injury: a randomised parallel-group trial with neuropsychological assessment

Studerus-Germann, Aline M ; Engel, Doortje C ; Stienen, Martin N ; von Ow, Dieter ; Hildebrandt, Gerhard ; Gautschi, Oliver P

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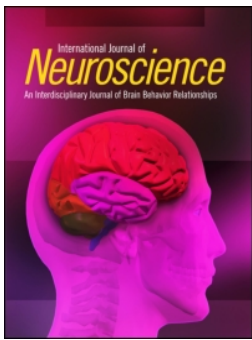
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Three versus seven days to return-to-work after mild traumatic brain injury: a randomised parallel-group trial with neuropsychological assessment

Aline M. Studerus-Germann^{1,2}; Doortje C. Engel, MD, PhD^{3,4}; Martin N. Stienen, MD^{3,6}; Dieter von Ow, MD⁵; Gerhard Hildebrandt, MD³; and Oliver P. Gautschi, MD^{3,6}

¹Division of Neuropsychology, Department of Neurology, State Hospital St.Gallen, St.Gallen, Switzerland

²Department of Psychopathology and Clinical Intervention, University of Zurich, Switzerland

³Department of Neurosurgery, Cantonal Hospital St.Gallen, St.Gallen, Switzerland

⁴Department of Neurosurgery, University Hospital Tübingen, Tübingen, Germany

⁵Emergency Department, Cantonal Hospital St.Gallen, St.Gallen, Switzerland

⁶Department of Neurosurgery and Faculty of Medicine, University Hospital Geneva, Geneva, Switzerland

Corresponding author: Oliver P. Gautschi, MD, Service de Neurochirurgie, Département des neurosciences cliniques, Hôpitaux Universitaires de Genève, Rue Gabrielle Perret-Gentil 4, 1205 Genève, Suisse, +41-79-55-33777, Email: ogautschi@gmail.com

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Abstract

Although most patients with a mild traumatic brain injury (mTBI) recover within days to weeks, some experience persistent physical, cognitive and emotional symptoms, often described as postconcussion syndrome (PCS). The optimal recovery time including return-to-work (RTW) after mTBI is unclear. In this single-centre parallel-group trial, patients assigned three days (3D-group) or seven days (7D-group) sick leave were compared with a comprehensive neuropsychological test battery including the Post Concussion Symptom Scale (PCSS) within one week, after three and twelve months post-injury. The influence of the effective time until RTW on postconcussional symptoms and cognitive performance was analyzed. The 3D-group rated significantly higher mean scores in some PCSS symptoms, tended to fulfil diagnosis criteria of PCS more often and showed better cognitive performance in several neuropsychological test scores than the 7D-group at all three time-points of follow-up. Overall, patients returned to work 11.35 days post injury, thus distinctly above both recommended sick leaves. There was a trend for longer sick leave in patients randomized into the 3D-group. Further analyses revealed that the group with an absolute RTW within one week showed lower symptom severity in fatigue at three and twelve months, less PCS and faster performance in fine motor speed at twelve months than the group with an absolute RTW after one week. Our data underline the heterogeneity of mTBI and shows that acute and sub-acute symptoms are not prognostic factors for neuropsychological outcome at one year. Later ability to work seems to be prognostic for long-term occurrence of PCS.

Key words: Mild traumatic brain injury; return-to-work; postconcussion syndrome; neuropsychological assessment; temporary work disability

Introduction

Approximately 100 to 300 per 100'000 individuals sustain a mild traumatic brain injury (mTBI) per year.(1) Although most patients with mTBI recover within days to weeks, some patients experience persistent physical, cognitive or behavioural symptoms, often referred as post-concussion syndrome (PCS).(2) The estimated prevalence of PCS varies widely, with 20 to 50% of mTBI patients reporting symptoms beyond three months and more than 10% still after one year.(3, 4) Persisting symptoms can include post-traumatic headache, sleep disturbance, fatigue, cognitive impairment, balance disorders, dizziness and affective disorders.(5) Persistent subjective cognitive complaints may disrupt the patients' social relationships and their ability to resume leisure and work-related activities.(6, 7)

While the exact pathophysiology of cognitive impairment after mTBI is still unclear,(8) it is generally accepted that functioning is most compromised for the first week after trauma.(9) During this period and beyond the brain is exceedingly vulnerable for further damage.(5, 8, 10-12) Strenuous cognitive and physical activities have been shown to exacerbate symptoms and thereby delay recovery.(13) Thus, current recommendations for mTBI patients generally include relative rest for the first two to five days without physical or cognitive exertion. However, bed-rest beyond the nightly sleep is generally not advised and patients are encouraged to resume normal activities as soon as possible.(12, 14)

The scientific evidence for recommendations for return-to-work (RTW) or resume activities of daily living (ADL) after mTBI is weak and varies greatly between one and 30 days.(15) Despite an overall high incidence of mTBI and PCS, no randomised trial has so far compared the duration of sick leave after mTBI and its impact on the incidence of PCS and subsequent cognitive outcome. The goal of this study was, therefore, to evaluate if the recommendation of a short (= three days) or intermediate (= seven days) time to RTW leads to a more favourable outcome regarding PCS and neuropsychological performance up to twelve months after mTBI and to evaluate the influence of the effective time to RTW on PCS and cognitive outcome.

Materials and methods

Consecutive mTBI patients from 18 to 64 years without focal neurological deficits presenting to the emergency department of the Cantonal Hospital of St.Gallen, Switzerland, were screened to participate in a single-centre prospective, randomised, parallel-group trial between August 2012 and December 2013. The study was approved by the local ethics committee (EKSG 11/122). All patients gave written informed consent prior to study inclusion. Mild TBI was defined with an initial Glasgow Coma Scale (GCS) of 13 to 15 at scene with loss of consciousness (LOC) lasting < 30 minutes and/or posttraumatic amnesia (PTA) < 24 hours. Computed tomography (CT) had to prove absence of pathological intracranial findings. Exclusion criteria included alcoholization (above 0.5 per mill blood alcohol), regular drug consumption, known psychiatric or neurological disease, previous (traumatic) brain injury, homelessness (due to the difficulty to contact patients for the scheduled follow-ups) and residence abroad, as well as major concurrent injuries.

After comprehensive study information and written informed consent, the neurosurgeon on call performed a physical baseline examination and completed a standardized concussion evaluation form.⁽¹⁶⁾ All recruited patients were randomly allocated to one of two study groups and received either a sick certificate for three days (3D-group) or seven days (7D-group) before being discharged from hospital. Previous to the start of recruitment, a list was generated with a random order of numbers corresponding to the two durations of sick leave and the neurosurgeon in charge of the randomization process was asked to take the subsequent number on the list when completing the sick certificate of a patient ready for discharge. Patients were not aware of the other group's time to RTW. The sick certificate intended to make a clear recommendation of days additional to the injury day until RTW or individual usual ADL, while it did not give further instructions on how to behave during the recommended days until RTW. Beside the study, usual recommendations on when to RTW was made by means of a doctor's certificate issued at the discretion of the neurosurgeon on call. As part of the standard care of our

hospital, an information sheet on mTBI was handed out to all mTBI patients, irrespective of the study group allocation, including information on common symptoms associated with mTBI, instructions on how to gradually return to everyday ADL as well as symptoms and signs, which call for a follow-up (FUP) with a medical doctor. The outcome was determined in three outpatient FUPs within one week (T1), at three (T2) and twelve months (T3) post-injury. All patients were asked when they effectively returned to work, the workload (in %) and the time until they reached their pre-injury workload eight and fourteen days post-injury by phone as well as during the neuropsychological FUPs. Of note, the term "RTW" was also used for students and homemakers, describing the time until the patients returned to their pre-injury occupation. A detailed neuropsychological assessment was performed using a battery of validated neuropsychological tests in German language as described in table 1. As a specific measure of PCS, patients rated the severity of 22 concussion symptoms for the preceding 24 hours on a 7-point Likert scale as part of the ImPACT, computing the Post Concussion Symptom Score (PCSS).(17) Additional to comparing raw data, validated normative data stratified for age were used to determine T-scores, and to calculate composite indices of neuropsychological domains (Table 1). Health-related quality of life (HRQoL) was measured using the Short-Form (SF) 36 health survey. The recruited patients did not receive any other intervention to facilitate rehabilitation as part of the study other than mentioned above.

The primary endpoint was the difference in the PCSS three months post-injury (T2) between the study groups. Secondary endpoints were the difference in neuropsychological test performance including domain-specific and overall performance, RTW, the rate of ICD-10 criteria for PCS (three or more reported symptoms out of seven core symptoms: headache, dizziness, trouble falling asleep, fatigue, difficulty concentrating, difficulty remembering and irritability) at T1 to T3, as well as the difference in PCSS at T1 and T3.

Statistical analyses

Statistical analyses were performed using SPSS 22.0. Group comparisons were analyzed with unpaired, two-tailed student t-tests or Mann-Whitney-U tests. Pearson's chi-squared test (χ^2) and the Fisher's exact test were used to evaluate the relationship between two categorical variables. P values < 0.05 were considered statistically significant.

Results

During the inclusion period a total of n=132 patients presented at the emergency department of the Cantonal Hospital St.Gallen with mTBI. N=102 patients were excluded from study participation due to inclusion or exclusion criteria or refusal to participate. The study had to be terminated in December 2013 due to logistic reasons. At this time point, 30 mTBI patients with a mean age of 35.0 years (18 to 55 years, 16 males and 14 females) were recruited. A complete neuropsychological assessment could be performed with n=27 patients at T1, n=24 at T2 and n=20 at T3. The reason for dropout in all cases was loss of motivation for further participation. One patient failed in the symptom validity test, screening for bad effort or malingering, and was thus excluded from further analysis. The occupational situation of the final study cohort of n=26 patients was: n=22 employed, n=3 students and n=1 homemaker. Baseline characteristics are depicted in table 2. The only significant difference was found in vocational class after primary education. A pathological overall result compared to normative data (T-score < 40) in the cognitive test battery was evident in three of 26 patients (11.5%) within one week, one of 23 patients (4.3%) at three months and none of the 19 patients at twelve months post-injury. The mean delay until RTW was 11.4 days, thus distinctly above both recommended sick leaves (Range 1 to 90 days). Table 3 shows the effective RTW time points. Notably only one patient of the whole sample (4.3%) complied with the assigned sick certificate. There was a trend for longer sick leave in patients randomized into the 3D-group (13.83 ± 24.33 versus (vs.) 8.64 ± 6.87 , $p=0.502$). Due to the lack of adherence to the sick certificate by the vast majority of both groups we were only able to evaluate whether the instruction to rest alters the outcome not whether increased rest changes the outcome.

Analysis of the primary endpoint

The group comparison did not show a significant difference in the total PCSS score between the D3-group and D7-group at three months post-injury (15.00 ± 16.07 vs. 9.42 ± 10.71 , $p=0.334$).

Analysis of the secondary endpoints - One week post-injury (T1)

The study groups did not differ significantly in the total PCSS score (27.62 ± 18.43 vs. 25.17 ± 18.53 , $p=0.744$). Analysis of subscores of the PCSS revealed significantly higher values in the symptom "nausea" for the D3-group (1.92 ± 2.06 vs. 0.33 ± 0.89 , $p=0.019$). There were no group differences in any of the other symptoms at T1. From the 3D-group, 84.6% (11 out of 13) met the ICD-10 criteria for PCS compared to 66.7% (8 out of 12) in the 7D-group ($p=0.378$). The results in the neuropsychological test battery showed significant group differences in four tests measuring two kinds of attentional functions, mental flexibility and visual memory (Table 4). The 3D-group showed better performance in the tests measuring divided attention, mental flexibility and visual memory, but more fluctuations in the selective attention test. There were no group differences in any of the other cognitive tests, the domain-specific composite indices, the total composite index, the SF-36, the severity of symptoms regarding depression or anxiety nor for an adjustment disorder. The 3D-group showed higher values in three of twenty subtests of the stress inventory (Table 5).

Three months post-injury (T2)

The 3D-group indicated significantly higher values of headache (2.55 ± 2.38 vs. 0.17 ± 0.58 , $p=0.005$), while no difference was found in any other PCSS symptoms. Figure 1 illustrates the group-scores for each of the items of the PCSS. From the 3D-group, 45.5% (5 out of 11) met the ICD-10 criteria for PCS compared to 33.3% (4 out of 12) in the 7D-group ($p=0.680$). The 3D-

group showed a faster or more accurate performance in four subtests that measure attentional functions and executive functions as well as in one composite score of the ImPACT (Table 6). In the SF-36 domain vitality, the 7D-group reached significantly higher values (16.92 ± 3.59 vs. 13.18 ± 4.22 ; $p=0.028$). There were no group differences in any of the other cognitive tests, the composite indices, the total composite index, or measures of depression, anxiety or adjustment disorder.

Twelve months post-injury (T3)

The 3D-group tended to show a higher mean PCSS score, but this group difference did not reach statistical significance (10.78 ± 11.12 vs. 4.90 ± 5.51 , $p=0.156$). Twelve months post-injury, the 3D-group reported higher values in the items fatigue (1.89 ± 1.76 vs. 0.30 ± 0.95 , $p=0.043$), sleeping less than usual (2.00 ± 2.06 vs. 0.00 ± 0.00 , $p=0.043$) and nervousness (1.44 ± 1.50 vs. 0.00 ± 0.00 , $p=0.043$). Four out of nine patients from the D3-group (44.4%) and one out of 10 patients in the 7D-group (10%) fulfilled the diagnostic criteria for PCS ($p=0.141$). Patients from the 3D-group reached a significantly better result in the visual motor speed composite of the ImPACT (39.43 ± 8.19 vs. 31.25 ± 5.44 , $p=0.028$). The groups did not differ significantly in any of the other assessed cognitive measures, the composite indices, the total composite index, including also the tests screening for a depression, anxiety or adjustment disorder as well as the SF-36.

As treated analysis: Effective time to RTW

For the analysis of effective time to RTW, 23 patients were evaluated. A frequency analysis showed that 52.2% of the group returned back to work within seven days. The assigned workload at RTW varied between 25 and 100%. The days until patients reached their pre-injury workload varied between one and over 365 days. Two patients did not return to their previous workload. Due to the lack of adherence to the recommended days of rest by the majority of study patients, an "as treated analysis" has been performed splitting the complete patient cohort by the median; thus into a group that returned to work within seven days ($\leq D7$ -group) and a group

returning to work after seven days (>D7-group). The two groups did not differ significantly in age, years of education, GCS status at inclusion, sex, vocational class or education (Table 7).

One week post-injury (T1)

There were no significant group differences regarding total PCSS scores between either groups (21.25 ± 15.31 vs. 29.30 ± 13.05 , $p=0.259$) or any of the PCS symptoms. Ninety per cent (9 out of 10) of patients in the >D7-group fulfilled the criteria for PCS compared to 66.7% (8 out of 12) in the \leq D7-group ($p=0.323$). There were no significant group differences between the \leq D7-group and the >D7-group in the neuropsychological test battery.

Three months post-injury (T2)

At T2, patients of the >D7-group showed a strong tendency to be more affected by symptoms measured with the PCSS score (16.33 ± 16.77 vs. 7.00 ± 6.77 , $p=0.074$). They showed significantly greater symptom severity in fatigue than patients of the \leq D7-group (2.60 ± 2.32 vs. 0.58 ± 1.08 , $p=0.029$). Patients of the >D7-group were twice as likely as patients of the \leq D7-group to fulfil the PCS criteria according to ICD-10 (54.5% vs. 25.0%, $p=0.214$). There were no significant group differences in all other cognitive tests and questionnaires.

Twelve months post-injury (T3)

At T3, patients of the >D7-group still showed a tendency to be more affected by PCSS symptoms (10.78 ± 11.48 vs. 4.90 ± 4.82 , $p=0.156$). The group returning to work after seven days showed again significantly higher symptom values in fatigue (13.30 ± 13.00 vs. 0.10 ± 0.32 , $p=0.017$). At T3, criteria for PCS were still fulfilled by 55.6% (5 out of 9) of the patients of the >D7-group compared to none of the patients in the \leq D7-group ($p=0.011$). Most of the neuropsychological

assessment was similar, except for worse performance of patients of the >D7-group on the fine motor speed task in the Grooved Pegboard (62.22 ± 8.39 vs. 53.70 ± 4.40 , $p=0.012$). There were no significant group differences in all other cognitive tests and questionnaires.

Discussion

This was a prospective randomized parallel-group trial investigating the influence of an early (3D) vs. intermediate (7D) recommendation to RTW after mTBI on more favourable neuropsychological recovery. The study groups did not differ significantly in terms of the PCSS three months post-injury. Therefore, no significant recommendation can be made for appropriate standardization of sick leave certificates. Limitations of our study include a small sample size due to which statistical power is limited and results can only be seen as tendencies. The chosen analytics did not appropriately include the longitudinal design. Despite randomization, there was an imbalance of vocational classes. The trial design had not anticipated a large lack of adherence of mTBI patients to the assigned RTW. The inclusion phase had to be terminated due to logistic reasons before achieving the necessary sample size.

At FUP time-point, there were no differences in the overall PCSS score between the two study groups. While the score was literally equal within the first week, tendencies for higher scores in the 3D-group at T2 and T3 post-injury became apparent. Higher symptom severity of nausea within one week post-injury could have a direct association to the assigned recommendation to RTW or ADLs after only three days of rest.(5, 8, 10-12) The observed group differences in the stress inventory suggest that patients in the 3D-group were more likely to pursue negative strategies (including mental preoccupation or rumination, resignation and aggression) to regulate stress than patients in the 7D-group. Negative coping strategies are potentially capable of further enforcing the negative development of symptoms post-injury and might explain the higher symptom severity in nausea (at T1), headache (at T2) and fatigue, as well as less sleep than usual and nervousness (at T3) in the 3D-group compared to the 7D-group. This is in line with previous findings that highly symptomatic patients with acquired brain injury primarily use

negative coping strategies.(18) The question remains if the group difference in vocational class could have influenced the use of stress regulation strategies between the groups. Our results suggest that more skilled workers tend to negative stress regulation strategies.

Patients of the 3D-group showed surprisingly better results in the vast majority of test scores that were different between the study groups. This would support the recommendation of a return back to pre-injury activities as soon as tolerated in recently published clinical practice guidelines.(19) Again, the higher mean vocational class of the 3D-group can play a role, as training in more skilled work usually leads to better results in cognitive test performance. Interestingly, however, no group differences in the duration of education or in the intelligence test were found, which are also prone to influence cognitive test performance. The sub-score fluctuations in the “Deux Barrage” test measuring selective and continuous attention at T1 was the only sub-score of the cognitive test battery, where the 7D-group reached a better result. This result represents more fluctuation during a 10-minute task, which can be a sign of fatigue, possibly due to higher symptom severity in patients with a short recommendation to RTW.

Despite a physician’s recommendation, nearly half of the patients did not feel ready to return to their pre-injury occupation at one week post-injury. A systematic review of RTW after mTBI summarized that most people are returning to work within three to six months after mTBI.(20) Both the median (7 days) and mean time until RTW (11.4 days) were considerably shorter in our sample than in the sample of Losoi et al., which had a median of 16 days and mean time of 26.1 (sub-sample with no PCS at twelve months) or 146.4 days to RTW (sub-sample with mild PCS at twelve months).(21) We believe that the mere recommendation of two certain times until RTW by means of a sick certificate did influence the duration until RTW positively, since it suggested to the patients that a rapid recovery from mTBI can be expected and RTW after a week is generally anticipated by the doctors.

While further research is needed to identify predictors of delayed RTW, our data indicate that patients with a real sick leave of more than seven days have a less favourable mid- and long-term prognosis. Our analysis showed without doubt two patterns of patients that differ greatly: early RTW with full workload and less PCS symptoms and later RTW with less workload and more PCS symptoms. Here, our results resemble the findings described in the literature.(19, 22) In our study cohort, the overall cognitive test performance was below the cut-off compared to normative data (T-score < 40) in three patients at T1, in one patient at T2 and in none of the patients at T3, which is in accordance with the current literature.(23) Interestingly, the subject with a pathological finding at T2 was one of the two patients who returned to work even before three recommended days. The two patients, who were not back to their previous workload at T3 did, however, not show impaired results (T-score < 40). These observations suggest a relative independence of RTW issues from cognitive test performance.

The results of the “as-treated analysis” suggest that a RTW within one week post-injury is more beneficial than a RTW after one week, but we cannot prove a causal relationship. The results from the “intention-to-treat analysis” indicate that an initial intermediate recommendation to RTW of seven days is more beneficial than a short recommendation of three days. With simultaneous consideration of both results, considering recent recommendations and taking our clinical experience into account, we recommend an initial recommendation to RTW of four to seven days, when an mTBI patient seeks doctor’s advice immediately after injury. Patients should be reassured that a good recovery from mTBI can generally be anticipated. If gradual RTW fails within three weeks post-injury, a physical or cognitive performance test should be performed, involving the skills of his pre-injury job as much as possible to objectify occurring symptoms and impairments. Following this, counselling by a psychologist, occupational therapist, physiotherapist or medical doctor is advised to educate and support him in the dealing with the persistent symptoms and possible cognitive and/or physical impairments taking the work environment into account and to accompany her/him in the gradual RTW.

Conclusions

There was no significant difference in the intention-to-treat analysis of the PCSS three months post-injury between patients randomized to resume work after three or seven days of sick leave. In the as-treated analysis, patients that returned to work within seven days post-injury resumed with a higher workload, showed less fatigue, less clinical signs of PCS as diagnosed according to ICD-10 criteria, and showed no neuropsychological impairment in the short-, mid- and long-term interval. Our data support the heterogeneity of mTBI and shows that acute and sub-acute symptoms are not prognostic factors for neuropsychological outcome at one year.

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Author Disclosure Statement

No competing financial interests exist.

References

1. Cassidy JD, Carroll LJ, Peloso PM, Borg J, von Holst H, Holm L, et al. Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *Journal of rehabilitation medicine*. 2004 Feb(43 Suppl):28-60. PubMed PMID: 15083870.
2. Ryan LM, Warden DL. Post concussion syndrome. *International review of psychiatry*. 2003 Nov;15(4):310-6. PubMed PMID: 15276952.
3. Faux S, Sheedy J, Delaney R, Riopelle R. Emergency department prediction of post-concussive syndrome following mild traumatic brain injury--an international cross-validation study. *Brain injury*. 2011;25(1):14-22. PubMed PMID: 21142827.

4. von Wild KR, Hannover MTBISC. Posttraumatic rehabilitation and one year outcome following acute traumatic brain injury (TBI): data from the well defined population based German Prospective Study 2000-2002. *Acta neurochirurgica Supplement*. 2008;101:55-60. PubMed PMID: 18642634.
5. Iverson GL. Outcome from mild traumatic brain injury. Current opinion in psychiatry. 2005 May;18(3):301-17. PubMed PMID: 16639155.
6. van der Naalt J. Prediction of outcome in mild to moderate head injury: a review. *Journal of clinical and experimental neuropsychology*. 2001 Dec;23(6):837-51. PubMed PMID: 11910548.
7. Yang CC, Tu YK, Hua MS, Huang SJ. The association between the postconcussion symptoms and clinical outcomes for patients with mild traumatic brain injury. *The Journal of trauma*. 2007 Mar;62(3):657-63. PubMed PMID: 17414343.
8. Giza CC, Hovda DA. The new neurometabolic cascade of concussion. *Neurosurgery*. 2014 Oct;75 Suppl 4:S24-33. PubMed PMID: 25232881. Pubmed Central PMCID: 4479139.
9. Studerus-Germann AM, Thiran JP, Daducci A, Gautschi OP. Diagnostic approaches to predict persistent post-traumatic symptoms after mild traumatic brain injury - a literature review. *The International journal of neuroscience*. 2016 Apr;126(4):289-98. PubMed PMID: 26000929.
10. Giza CC, Hovda DA. The Neurometabolic Cascade of Concussion. *Journal of athletic training*. 2001 Sep;36(3):228-35. PubMed PMID: 12937489. Pubmed Central PMCID: 155411.
11. McCrea M, Guskiewicz KM, Marshall SW, Barr W, Randolph C, Cantu RC, et al. Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *Jama*. 2003 Nov 19;290(19):2556-63. PubMed PMID: 14625332.
12. Silverberg ND, Iverson GL. Is rest after concussion "the best medicine?": recommendations for activity resumption following concussion in athletes, civilians, and military service members. *The Journal of head trauma rehabilitation*. 2013 Jul-Aug;28(4):250-9. PubMed PMID: 22688215.
13. McCrory P, Makdissi M, Davis G, Collie A. Value of neuropsychological testing after head injuries in football. *British journal of sports medicine*. 2005 Aug;39 Suppl 1:i58-63. PubMed PMID: 16046357. Pubmed Central PMCID: 1765310.
14. Guskiewicz KM, Bruce SL, Cantu RC, Ferrara MS, Kelly JP, McCrea M, et al. National Athletic Trainers' Association Position Statement: Management of Sport-Related Concussion. *Journal of athletic training*. 2004 Sep;39(3):280-97. PubMed PMID: 15514697. Pubmed Central PMCID: 522153.

15. De Kruijk JR, Twijnstra A, Meerhoff S, Leffers P. Management of mild traumatic brain injury: lack of consensus in Europe. *Brain injury*. 2001 Feb;15(2):117-23. PubMed PMID: 11260762.
16. Gioia GA, Collins M, Isquith PK. Improving identification and diagnosis of mild traumatic brain injury with evidence: psychometric support for the acute concussion evaluation. *The Journal of head trauma rehabilitation*. 2008 Jul-Aug;23(4):230-42. PubMed PMID: 18650767.
17. Maroon JC, Lovell MR, Norwig J, Podell K, Powell JW, Hartl R. Cerebral concussion in athletes: evaluation and neuropsychological testing. *Neurosurgery*. 2000 Sep;47(3):659-69; discussion 69-72. PubMed PMID: 10981754.
18. Velikonja D, Warriner EM, Coulson S, Brum C. The relationship between coping styles and affective/behavioural symptoms among individuals with an acquired brain injury. *Brain injury*. 2013;27(2):158-68. PubMed PMID: 23324048.
19. Marshall S, Bayley M, McCullagh S, Velikonja D, Berrigan L, Ouchterlony D, et al. Updated clinical practice guidelines for concussion/mild traumatic brain injury and persistent symptoms. *Brain injury*. 2015;29(6):688-700. PubMed PMID: 25871303.
20. Cancelliere C, Kristman VL, Cassidy JD, Hincapie CA, Cote P, Boyle E, et al. Systematic review of return to work after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Archives of physical medicine and rehabilitation*. 2014 Mar;95(3 Suppl):S201-9. PubMed PMID: 24581906.
21. Losoi H, Silverberg N, Waljas M, Turunen S, Rosti-Otajarvi E, Helminen M, et al. Recovery from Mild Traumatic Brain Injury in Previously Healthy Adults. *Journal of neurotrauma*. 2015 Oct 6. PubMed PMID: 26437675.
22. Majerske CW, Mihalik JP, Ren D, Collins MW, Reddy CC, Lovell MR, et al. Concussion in sports: postconcussive activity levels, symptoms, and neurocognitive performance. *Journal of athletic training*. 2008 May-Jun;43(3):265-74. PubMed PMID: 18523563. Pubmed Central PMCID: 2386420.
23. Karr JE, Areshenkoff CN, Garcia-Barrera MA. The neuropsychological outcomes of concussion: a systematic review of meta-analyses on the cognitive sequelae of mild traumatic brain injury. *Neuropsychology*. 2014 May;28(3):321-36. PubMed PMID: 24219611.
24. Reitan RM. Trail Making Test: Manual for administration and scoring. Reitan Neuropsychology Laboratory. 1992.
25. Zimmermann P, Fimm B. Testbatterie zur Aufmerksamkeitsprüfung (TAP). Handbuch Version 17. 2002;Herzogenrath, Deutschland.
26. Zazzo R. Test des deux barrages. EAP. 1960.

27. von Aster M, Neubauer A, Horn R. Wechsler Intelligenztest für Erwachsene (WIE). Deutschsprachige Bearbeitung und Adaptation des WAIS-III von David Wechsler. 2006;Frankfurt/Main, Germany: Harcourt Test Services.
28. Schellig D, Schächtele B. Visueller und Verbaler Merkfähigkeitstest (VVM). Swets & Zeitlinger, BV, Swets Test Services, Frankfurt am Main. 2001.
29. Aschenbrenner S, Tucha O, Lange KW. Regensburger Wortflüssigkeits-Test: RWT. Hogrefe, Verlag für Psychologie. 2000.
30. Regard M, Strauss E, Knapp P. Children's production on verbal and non-verbal fluency tasks. Perceptual and motor skills. 1982 Dec;55(3 Pt 1):839-44. PubMed PMID: 7162920.
31. Balzer C, Berger JM, Caprez G, Gonser A, Gutbrod K, Keller M. Materialien und Normwerte für die neuropsychologische Diagnostik (MNND). Normdaten, Rheinfelden. 2011.
32. Stroop J. Studies of interference in serial verbal reaction. J Experimental Psychology. 1935;18:643-62.
33. Trites R. Grooved pegboard test. Royal Ottawa Hospital. 1989.
34. Green P. Green's Medical Symptom Validity Test (MSVT) for Microsoft Windows. Edmonton: Green's Publishing. 2004.
35. Hautzinger M, Keller F, Kühner C. BDI-II. Beck Depression-Inventar Revision. Bern: Harcourt Test Services. 2006.
36. Margraf J, Ehlers A. Das Beck Angst Inventar (BAI). Pearson Assessment & Information GmbH. 2007.
37. Maercker A, Einsle F, Kollner V. Adjustment disorders as stress response syndromes: a new diagnostic concept and its exploration in a medical sample. Psychopathology. 2007;40(3):135-46. PubMed PMID: 17284941.
38. Bullinger M, Kirchberger I, Ware J. Der deutsche SF-36 Health Survey. Übersetzung und psychometrische Testung eines krankheitsübergreifenden Instruments zur Erfassung der gesundheitsbezogenen Lebensqualität. J Publ Health. 1995;3(1):21-36.
39. Janke W, Erdmann G. 4. überarbeitete und erweiterte Auflage. SFV Stressverarbeitungsfragebogen; Stress, Stressverarbeitung und ihre Erfassung durch ein mehrdimensionales Testsystem. 2008;Hogrefe Verlag.

Figure 1. Results from the 3D-group versus the 7D-group on the Post Concussion Symptom Scale (PCSS) at T2. A higher score reflects a higher symptom severity (six was the highest selectable value, zero means the patient does not experience a symptom). Note that except for headache, no significant difference in any of the items was found.

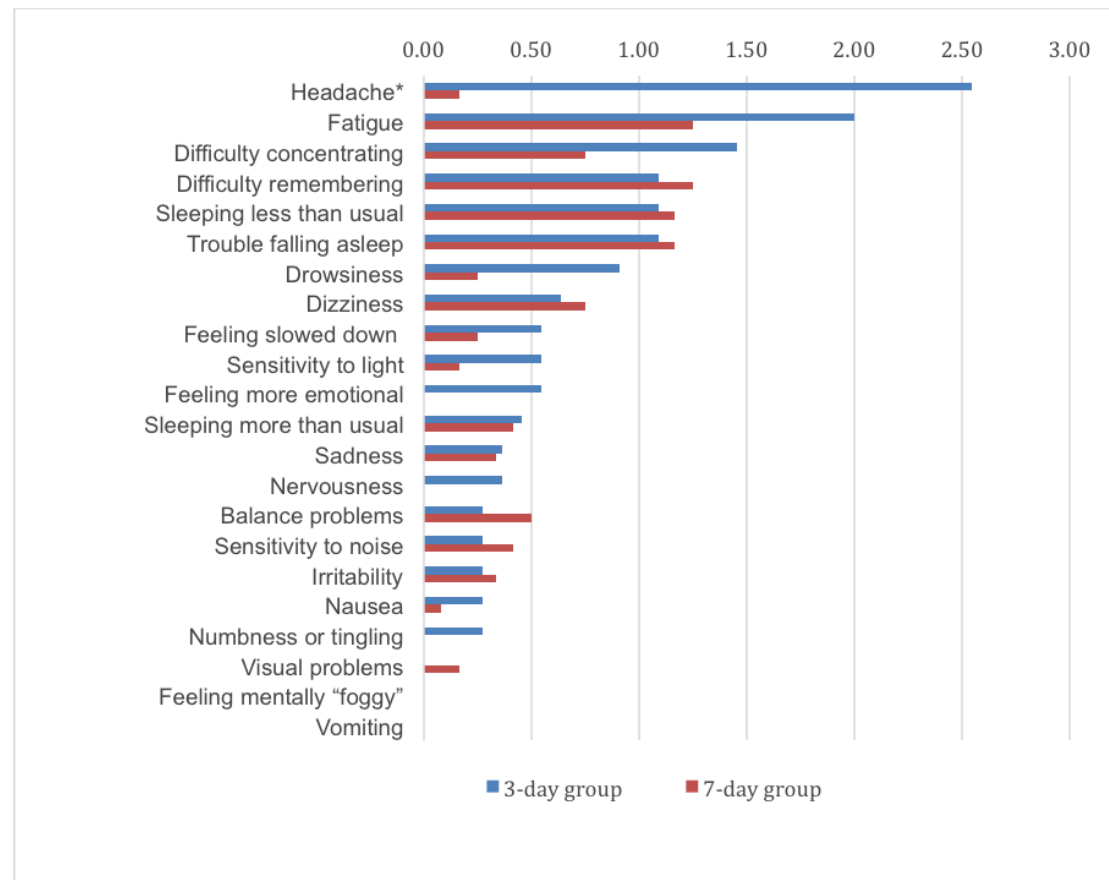


Table 1. Neuropsychological measures. Abbreviations: ANMD = Adjustment Disorder New Module; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; ImPACT = Immediate Post-Concussion Assessment and Cognitive Testing; FPT = Five-Point Test; MNND = “Materialien und Normwerte für die Neuropsychologische Diagnostik” in English: materials and norm values for the neuropsychological diagnostics; MSVT = Medical Symptom Validity Test; PCSS = Post Concussion Symptom Score; RWT = “Regensburger Wortflüssigkeits-Test” in English: Regensburg word fluency test; SF = short-form; SVF = stress inventory; TAP = Test of Attentional Performance; TMT = Trail Making Test; VVM = Visual and Verbal retentiveness test; WAIS = Wechsler Adult Intelligence Scale; WIE = German version of the Wechsler Adult Intelligence Scale.

Measured cognitive domain Measure cognitive function	Test name / battery (reference)
Attention	
Speed of processing / reaction time	<ul style="list-style-type: none"> ▪ TMT A (Reitan, 1958²⁷) ▪ Subtest Alertness from the TAP (Zimmermann and Fimm, 2002²⁸) ▪ ImPACT (Maroon et al., 2000²⁹)
Selective sustained attention	<ul style="list-style-type: none"> ▪ Deux Barrages (Zazzo, 1960³⁰)
Divided Attention	<ul style="list-style-type: none"> ▪ Subtest Divided Attention from TAP
Covert shift of attention	<ul style="list-style-type: none"> ▪ Subtest Covert shift of attention from TAP
Memory	
Verbal short-time memory	<ul style="list-style-type: none"> ▪ Subtest Digits Forward from the WIE (German version of WAIS-III; von Aster et al., 2006³¹)
Verbal working memory	<ul style="list-style-type: none"> ▪ Subtest Backward Span from WIE³¹
Visual and verbal retentiveness	<ul style="list-style-type: none"> ▪ VVM (Schellig & Schächtele, 2001³²) ▪ ImPACT
Executive functions	
Verbal fluency	<ul style="list-style-type: none"> ▪ RWT (Aschenbrenner et al., 2000³³)
Design fluency	<ul style="list-style-type: none"> ▪ Adaption of the FPT (Regard et al., 1982³⁴) from the test-battery MNND (Balzer et al., 2011³⁵)
Cognitive processing / Interference susceptibility	<ul style="list-style-type: none"> ▪ German adaption of the Stroop Color and Word Test (Stroop, 1935³⁶) from the test-battery MNND (Balzer et al., 2011³⁵)
Cognitive flexibility	<ul style="list-style-type: none"> ▪ TMT B (Reitan, 1958²⁷)

Fine motor speed	▪ Grooved Pegboard (Trites, 1989 ³⁷)
Intellectual capacity	▪ Subtest Similarities from WIE ¹
Effort / Malingering	▪ Green's MSVT (Green, 2004 ³⁸)
Psychiatric symptoms	
Post-concussion symptoms	▪ PCSS as part of ImPACT
Depression	▪ BDI-II (Hautzinger et al., 2006 ³⁹)
Anxiety	▪ BAI (Margraf and Ehlers, 2007 ⁴⁰)
Adjustment Disorder	▪ ANMD (Maercker et al., 2007 ⁴¹)
Quality of life / state of health	▪ German translation of the Health Survey SF-36 (Bullinger et al., 1995 ⁴²)
Stress regulation / Coping	▪ SVF-120 ² (Janke and Erdmann, 2008 ⁴³)

¹ This test was not performed at the second follow-up to prevent from practice effect.

² This questionnaire was only filled in once before T1 since stress regulation is said to be stable.

Table 2. Demographics of patients with mild traumatic brain injury (mTBI), as randomized in a group with either 3-day or 7-day sick leave post-injury.

Parameter	Study groups		p-value
	3D-group	7D-group	
Age (years), M (SD)	32.46 (11.99)	40.00 (14.63)	0.164
Gender			0.050
Male	4 (30.8%)	9 (69.2%)	
Female	9 (69.2%)	4 (30.8%)	
Education (years), M (SD)	12.81 (1.97)	12.31 (3.13)	0.630
Vocational class*			0.039
1 – 3	4 (30.8%)	2 (15.4%)	
4 – 6	8 (61.5%)	4 (30.8%)	
7 – 9	1 (7.7%)	7 (53.8%)	
GCS at inclusion			0.372
15	11 (84.6%)	9 (69.2%)	
14	2 (15.4%)	4 (30.8%)	
Total	n=13 (100%)	n=13 (100%)	

M= Mean. SD = Standard deviation. GCS= Glasgow Coma Score

* Based on the International Standard Classification of Occupations (ISCO-88).

Table 3. Actual return-to-work in patients randomized to return-to-work after 3 days (3D-group) or 7 days of sick leave (7D-group).

	Before recommendation	According to recommendation	After recommendation
3D-group	2 (8.7 %) M: 1.5, SD: 0.71 Range: 1 to 2 days	0	10 (43.5 %) M: 16.30, SD: 26.13 Range: 4 to 90 days
7D-group	5 (21.7 %) M: 4.00, SD: 0.71 Range: 3 to 5 days	1 (4.3 %)	5 (21.7 %) M: 13.60, SD: 7.70 Range: 8 to 27 days
N=23 (100%)	7 (30.4 %)	1 (4.3 %)	15 (65.2 %)

Group indicates the randomized days of return-to-work certificate. M = Mean of days going back to work. SD = Standard deviation.

Table 4. Results from the neuropsychological test battery with significant group differences at T1 within one week post-injury. Lower values indicate better performance on the following tests: divided attention, selective sustained attention, mental flexibility. Higher values indicate better performance on the following test: Visual and verbal retentiveness.

Measured cognition (unit) – test name	3D-group <i>M (SD)</i>	7D-group <i>M (SD)</i>	<i>t</i>	<i>p</i>
Divided attention visual cue (number of omissions) - TAP	0.50 (0.67)	1.69 (1.89)	- 2,13	0.049
Selective sustained attention (fluctuations) - <i>Deux Barrage</i>	14.92 (6.53)	9.77 (3.03)	2.56	0.017
Mental flexibility (time of completion in s) - <i>TMT B</i>	52.17 (14.25)	78.46 (31.72)	- 2,63	0.015
Visual retention late recall (number of points achieved) - VVM	11.23 (5.50)	7.08 (5.11)	2.14	0.042

Group indicates the randomized days of return-to-work certificate. RT= reaction time. TAP= Test of Attentional Performance. TMT= Trail Making Test. MNND= Materials and Norm values for the Neuropsychological Diagnostics. M= Mean. SD = Standard deviation.

Table 5. Significant group differences in stress regulation strategies measured with SVF-120 at the time point T2 (three months post-injury).

Factors	3D-group <i>M (SD)</i>	7D-group <i>M (SD)</i>	<i>t</i>	<i>p</i>
Mental preoccupation / rumination	17.80 (5.07)	12.18 (5.78)	2.36	0.029
Resignation	10.00 (5.21)	4.91 (3.78)	2.58	0.018
Aggression	9.90 (4.04)	5.09 (4.44)	2.59	0.018
Negative strategies	11.67 (4.15)	7.75 (3.87)	2.13	0.048

Group indicates the randomized days of return-to-work certificate. M= Mean. SD = Standard deviation.

Table 6. Results from the neuropsychological test battery with significant group differences at T2 three months post-injury. Lower values indicate better performance on the following tests: *TMT A, Deux Barrage, TMT B*. Higher values indicate better performance on the following tests: *Design Fluency of MNND, ImPACT*.

Measured cognition (unit) – test name	3D-group <i>M (SD)</i>	7D-group <i>M (SD)</i>	<i>t</i>	<i>p</i>
Processing speed (time of completion in s) - <i>TMT A</i>	19.18 (7.11)	26.58 (7.80)	- 2,37	0.027
Selective attention (omissions/min) - <i>Deux Barrage</i>	0.85 (1.03)	2.28 (1.62)	- 2,51	0.020
Design fluency (total correct items) – <i>Design Fluency of MNND</i>	41.73 (8.59)	33.50 (7.88)	2.40	0.026
Mental flexibility (time of completion in s) - <i>TMT B</i>	49.09 (21.84)	71.50 (25.09)	- 2,28	0.034
Visual motor speed composite - ImPACT	36.25 (12.32)	25.32 (9.71)	2.38	0.027

Group indicates the randomized days of return-to-work certificate. RT= reaction time. TAP= Test of Attentional Performance. TMT= Trail Making Test. MNND= Materials and Norm values for the Neuropsychological Diagnostics. M= Mean. SD = Standard deviation.

Table 7. Demographics of patients with mild traumatic brain injury (mTBI), according to the “as treated” group assignment into a group that returned to work within seven days ($\leq 7D$ -group) and a group that returned to work after seven days post-injury ($>7D$ -group).

Parameter	<i>As treated groups</i>		p-value
	$\leq 7D$ -group	$>7D$ -group	
Age (years), M (SD)	38.33 (15.52)	38.00 (11.15)	0.953
Gender			0.220
Male	8 (66.7%)	4 (36.4%)	
Female	4 (33.3%)	7 (63.6%)	
Education (years), M (SD)	12.58 (1.99)	13.50 (3.01)	0.394
Vocational class*			0.340
1 – 3	3 (25%)	3 (27.3%)	
4 – 6	5 (41.7%)	5 (45.5%)	
7 – 9	4 (33.3%)	3 (27.3%)	
GCS at inclusion			0.559
15	10	8	
14	2	3	
Time to return-to-work (days), M (SD)	4.25 (1.82)	19.09 (24.16)	0.069
Total	n=12 (100%)	n=11 (100%)	

M= Mean. SD = Standard deviation. GCS= Glasgow Coma Score.

* Based on the International Standard Classification of Occupations (ISCO-88).